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GULF WAR ILLNESSES**Enhanced Monitoring of
Clinical Progress and of
Research Priorities Needed**

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Mr. Chairman and Members of the Subcommittee:

We are pleased to be here today to discuss the results of our study on the government's clinical care and medical research programs relating to illnesses that members of the armed forces might have contracted as a result of their service in the Persian Gulf War.¹ Our report responds to the mandate of the fiscal year 1997 defense authorization act. Specifically, we will discuss three issues: (1) the efforts of the Department of Defense (DOD) and the Department of Veterans' Affairs' (VA) to assess the quality of treatment and diagnostic services provided to Gulf War veterans and their provisions for follow-up of initial examinations, (2) the government's research strategy to study the veterans' illnesses and the methodological problems posed in its studies, and (3) the consistency of key official conclusions with available data on the causes of the veterans' illnesses.

We will summarize our findings on the three issues we reviewed and then provide more detail. Regarding the first issue, although efforts have been made to diagnose veterans' problems and care has been provided to many eligible veterans, neither DOD nor VA has systematically attempted to determine whether ill Gulf War veterans are any better or worse today than when they were first examined.

On the second issue, we found that the majority of the research has focused on the epidemiological study of the prevalence and cause of Gulf War illnesses rather than the diagnosis, treatment, and prevention of them. While this epidemiological research will provide descriptive data on veterans' illnesses, methodological problems are likely to prevent researchers from providing precise, accurate, and conclusive answers regarding the causes of veterans' illnesses. Without accurate exposure information, the investment of millions of dollars in further epidemiological research on the risk factors (or potential causes) for veterans' illnesses may result in little return.

Regarding the third issue, support for some official conclusions regarding stress, leishmaniasis (a parasitic infection), and exposure to chemical agents was weak or subject to alternative interpretations.

Background

Before turning to the results of our work in detail, let me briefly provide some background information and discuss the methodology we used for

¹Gulf War Illnesses: Improved Monitoring of Clinical Progress and Reexamination of Research Emphasis Are Needed (GAO/NSIAD-97-163, June 23, 1997).

our study. During their deployment associated with the Persian Gulf War, many of the approximately 700,000 veterans of the Gulf War may have been exposed to a variety of potentially hazardous substances. These substances include compounds used to decontaminate equipment and protect it against chemical agents, fuel used as a sand suppressant in and around encampments, fuel oil used to burn human waste, fuel in shower water, leaded vehicle exhaust used to dry sleeping bags, depleted uranium, parasites, pesticides, drugs to protect against chemical warfare agents (such as pyridostigmine bromide), and smoke from oil-well fires. Moreover, DOD acknowledged in June 1996 that some veterans may have been exposed to the nerve agent sarin following the postwar demolition of Iraqi ammunition facilities.

Many of these veterans have complained of a wide array of symptoms and disabling conditions since the end of the war in 1991. Some fear that they are suffering from chronic disabling conditions because of exposure to chemicals, pesticides, and other agents used during the war with known or suspected health effects. Accordingly, both DOD and VA established programs through which Gulf War veterans could receive medical examinations and diagnostic services. From 1992 to 1994, VA participants received a regular physical examination with basic laboratory tests. In 1994, VA established a standardized examination to obtain information about exposures and symptoms related to diseases endemic to the Gulf region and to order specific tests to detect the "biochemical fingerprints" of certain diseases. If a diagnosis was not apparent, veterans could receive up to 22 additional tests and additional specialty consultations. In addition, if the illness defied diagnosis, the veterans could be referred to one of four VA Persian Gulf referral centers.

DOD initiated its Comprehensive Clinical Evaluation Program in June 1994. It was primarily intended to provide diagnostic services similar to those of the VA program and employed a similar clinical protocol. However, the VA program was among the first extensive efforts to gather data from veterans regarding the nature of their problems and the types of hazardous agents to which they might have been exposed.

Methodology

To address our first evaluation question—the extent of DOD's clinical follow-up and monitoring of treatment and diagnostic services—we reviewed literature and agency documents and conducted structured interviews with DOD and VA officials. We asked questions designed to identify and contrast their methods for monitoring the quality and

outcomes of their treatment and diagnostic programs and the health of the registered veterans.

The second objective concerns the coherence of the Persian Gulf Veterans Coordinating Board's (PGVCB) research strategy. To answer this question, we conducted a systematic review of pertinent literature and agency documents and reports. We interviewed representatives of the PGVCB's² Research Working Group and officials of VA and DOD. We also surveyed primary investigators of ongoing epidemiological studies.

Because different methodological standards apply to various types of research and because the overwhelming majority of federally sponsored research is categorized as epidemiological, we limited our survey to those responsible for ongoing epidemiological studies. With the help of an expert epidemiological consultant, we devised a questionnaire to assess critical elements of these studies (including the quality of exposure measurement, specificity of case definition, and steps to ensure adequate sample size) and to identify specific problems that the primary investigators may have encountered in implementing their studies. We interviewed primary investigators for 31 (72 percent) of the 43 ongoing epidemiological studies identified by PGVCB in the November 1996 plan. We also reviewed and categorized descriptions of all 91 projects identified by April 1997, based on their apparent focus and primary objective. Finally, to review the progress of major ongoing research efforts, we visited the Walter Reed Army Institute of Research, the Naval Health Research Center, and two of VA's Environmental Hazards Research Centers.

To address the third objective, we reviewed major conclusions of the PGVCB and the Presidential Advisory Committee on Gulf War Veterans' Illnesses to determine the strength of evidence supporting major conclusions. The purpose of this review was not to critique PGVCB's or the Presidential Advisory Committee's efforts, per se, in this regard, but rather to describe the amount of knowledge about Gulf War illnesses that has been generated by research 6 years after the war. We reviewed these conclusions because they are the strongest statements that we have come across on these matters by any official body. The Presidential Advisory Committee's report was significant because the panel included a number of recognized experts who were assisted by a large staff of scientists and attorneys. In addition, the Committee conducted an extensive review of the research. Thus, we believed that evaluating these conclusions would

²The PGVCB, comprised of the Secretaries of Defense, Veterans Affairs, and Health and Human Services, is charged with coordinating the federal response to Gulf War veterans' illnesses

provide important evidence about how fruitful the federal research has been thus far. We addressed this objective by reviewing extant scientific literature and consulting experts in the fields of epidemiology, toxicology, and medicine.

Because of the scientific and multidisciplinary nature of this issue, we ensured that staff conducting the work had appropriate backgrounds in epidemiology, psychology, environmental health, toxicology, engineering, weapon design, and program evaluation and methodology. In addition, we used in-house expertise in chemical and biological warfare and military health care systems. Also, medical experts reviewed our work. Moreover, we held extensive discussions with experts in academia in each of the substantive fields relevant to this issue. Finally, we talked to a number of the authors of the studies that we cited in this report to ensure that we correctly interpreted their findings and had independent experts review our draft report.

Our work was completed between October 1996 and April 1997 in accordance with generally accepted government auditing standards.

DOD and VA Have No Systematic Approach to Monitoring Gulf War Veterans' Health After Initial Examination

Over 100,000 of the approximately 700,000 Gulf War veterans have participated in DOD and VA health examination programs. Of those veterans examined by DOD and VA, nearly 90 percent have reported a wide array of health complaints and disabling conditions. The most commonly reported symptoms in VA and DOD registries include fatigue, muscle and joint pain, gastrointestinal complaints, headache, skin rash, depression, neurologic and neurocognitive impairments, memory loss, shortness of breath, and sleep disturbances.

Officials of both DOD and VA have claimed that regardless of the cause of veterans' illnesses, veterans are receiving appropriate and effective symptomatic treatment. Both agencies have tried to measure or ensure the quality of veterans' initial examinations through such mechanisms as training and standards for physician qualification. However, these mechanisms do not ensure a given level of effectiveness for the care provided or permit identification of the most effective treatments.³

We found that neither DOD nor VA has mechanisms for monitoring the quality, appropriateness, or effectiveness of these veterans' care or clinical

³See VA Health Care: Observations on Medical Care Provided to Persian Gulf Veterans (GAO/T-HEHS-97-158, June 19, 1997).

progress after their initial examination and they described no plans to establish such mechanisms. VA officials involved in administering the registry program told us that they regarded monitoring the clinical progress of registry participants as a separate research project, and the manager of DOD's Clinical Care and Evaluation Program made similar comments. We believe that such monitoring is important because (1) undiagnosed conditions are not uncommon among ill veterans, (2) treatment for veterans with undiagnosed conditions is based on their symptoms, and (3) veterans with undiagnosed conditions or multiple diagnoses may see multiple providers. Without follow-up of their treatment, DOD and VA cannot say whether these ill veterans are any better or worse today than when they were first examined.

Federal Research Strategy Lacks a Coherent Approach

Federal research on Gulf War veterans' illnesses and factors that might have caused their problems has not been pursued proactively. Although these veterans' health problems began surfacing in the early 1990s, the vast majority of research was not initiated until 1994 or later. And much of this research was associated with legislation or external reviewers' recommendations. This 3-year delay has complicated the task facing researchers and has limited the amount of completed research currently available. Although at least 91 studies have received federal funding, over 70, or four-fifths, of the studies are not yet complete, and the results of some studies will not be available until after 2000.

We found that some hypotheses received early emphasis, while some hypotheses were not initially pursued. While research on exposure to stress received early emphasis, research on low-level chemical exposure was not pursued until legislated in 1996. The failure to fund such research cannot be traced to an absence of investigator-initiated submissions. According to DOD officials, three recently funded proposals on low-level chemical exposure had previously been denied funds. We found that additional hypotheses were pursued in the private sector. A substantial body of research suggests that low-level exposure to chemical warfare agents or chemically related compounds, such as certain pesticides, is associated with delayed or long-term health effects.

Regarding delayed health effects of organophosphates, the chemical family used in many pesticides and chemical warfare agents, there is evidence from animal experiments, studies of accidental human exposures, and epidemiological studies of humans that low-level exposures to certain organophosphorus compounds, including sarin nerve

agents to which some of our troops may have been exposed, can cause delayed, chronic neurotoxic effects.⁴

It has been suggested that the ill-defined symptoms experienced by Gulf War veterans may be due in part to organophosphate-induced delayed neurotoxicity.⁵ This hypothesis was tested in a privately supported epidemiological study of Gulf War veterans.⁶ In addition to clarifying the patterns among veterans' symptoms by use of statistical factor analysis, this study indicated that vague symptoms of the ill veterans are associated with objective brain and nerve damage compatible with the known chronic effects of exposures to low levels of organophosphates.⁷ It further linked the veterans' illnesses to exposure to combinations of chemicals, including nerve agents, pesticides in flea collars, N,N-diethyl-m-toluamide (DEET) in highly concentrated insect repellents, and pyridostigmine bromide tablets.

Toxicological research indicates that agents like pyridostigmine bromide, which Gulf War veterans took to protect themselves against the immediate, life-threatening effects of nerve agents, may alter the metabolism of organophosphates in ways that activate their delayed, chronic effects on the brain.⁸ Moreover, exposure to combinations of organophosphates and related chemicals like pyridostigmine or DEET has

⁴Sarin has been used as a chemical warfare agent since World War II, most recently during the Iran-Iraq war, and by terrorists in Japan.

⁵R. W. Haley et al., "Preliminary Findings of Studies on the Gulf War Syndrome," Presentations to the Intergovernmental Coordinating Board for the Gulf War Illness and the Staff of the Presidential Advisory Committee on Gulf War Veterans' Illnesses, September 16, 1995; R. W. Haley, "Organophosphate-Induced Delayed Neurotoxicity," Internal Medicine Grand Rounds, University of Texas Southwestern Medical Center, Dallas, Texas, October 10, 1996; and G. A. Jamal et al., "The Gulf War Syndrome: Is There Evidence of Dysfunction in the Nervous System?" Journal of Neurology, Neurosurgery and Psychiatry, Vol. 60 (1996), pp. 449-451.

⁶This research, conducted at the University of Texas Southwestern Medical Center, has been supported in part by funding from the Perot Foundation.

⁷R. W. Haley et al., "Is There a Gulf War Syndrome? Searching for Syndromes by Factor Analysis of Symptoms," Journal of the American Medical Association, vol. 277 (1997), pp. 215-222; R. W. Haley et al., "Evaluation of Neurologic Function in Gulf War Veterans: A Blinded Case-Control Study," Journal of the American Medical Association, vol. 277 (1997), pp. 223-230; and R. W. Haley et al., "Self-reported Exposure to Neurotoxic Chemical Combinations in the Gulf War: A Cross-sectional Epidemiologic Study," Journal of the American Medical Association, vol. 277 (1997), pp. 231-237.

⁸C. N. Pope and S. Padilla, "Potentiation of Organophosphorus Delayed Neurotoxicity," Journal of Toxicology and Environmental Health, vol. 31 (1990), pp. 261-273.

been shown in animal studies to be far more likely to cause morbidity and mortality than any of the chemicals acting alone.⁹

We found that the bulk of ongoing federal research on Gulf War veterans' illnesses focuses on the epidemiological study of the prevalence and cause of the illnesses. It is important to note that in order to conduct such studies, investigators must follow a few basic, generally accepted principles.

First, they must specify diagnostic criteria to (1) reliably determine who has the disease or condition being studied and who does not and (2) select appropriate controls (people who do not have the disease or condition).

Second, the investigators must have valid and reliable methods of collecting data on the past exposure(s) of those in the study to possible factors that may have caused the symptoms. The need for accurate, dose-specific exposure information is particularly critical when low-level or intermittent exposure to drugs, chemicals, or air pollutants is possible. It is important not only to assess the presence or absence of exposure but also to characterize the intensity and duration of exposure.

We found that the ongoing epidemiological federal research suffered from two methodological problems: a lack of a case definition, and absence of accurate exposure data. Without valid and reliable data on exposures and the multiplicity of agents to which the veterans were exposed, researchers will likely continue to find it difficult to detect relatively subtle effects and to eliminate alternative explanations for Gulf War veterans' illnesses. Prevalence data can be useful, but it requires careful interpretation in the absence of better information on the factors to which veterans were exposed. While multiple federally funded studies of the role of stress in the veterans' illnesses have been done, basic toxicological questions regarding the substances to which they were exposed remain unanswered.

We found that federal researchers studying Gulf War illnesses have faced several methodological challenges and encountered significant problems in linking exposures or potential causes to observed illnesses or symptoms. For example:

⁹M. B. Abou-Donia et al., "Increased Neurotoxicity Following Concurrent Exposure to Pyridostigmine Bromide, DEET, and Chlorpyrifos," *Fundamentals of Applied Toxicology*, vol. 34 (1996), pp. 201-222, and M. B. Abou-Donia et al., "Neurotoxicity Resulting From Coexposure to Pyridostigmine Bromide, DEET, and Permethrin," *Journal of Toxicology and Environmental Health*, vol. 48 (1996), pp. 35-56.

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- Researchers have found it extremely difficult to gather information about exposures to such things as oil-well fire smoke and insects carrying infection.
 - DOD has acknowledged that records of the use of pyridostigmine bromide and vaccinations to protect against chemical/biological warfare exposures were inadequate.
 - Gulf War veterans were typically exposed to a wide array of agents, making it difficult to isolate and characterize the effects of individual agents or to study their combined effects.
 - Most of the epidemiological studies on Gulf War veterans' illnesses have relied only on self-reports for measuring most of the agents to which veterans may have been exposed.
 - The information gathered from Gulf War veterans years after the war may be inaccurate or biased. There is often no straightforward way to test the validity of self-reported exposure information, making it impossible to separate bias in recalled information from actual differences in the frequency of exposures. As a result, findings from these studies may be spurious or equivocal.
 - Classifying the symptoms and identifying illnesses of Gulf War veterans have been difficult. From the outset, symptoms reported by veterans have been varied and difficult to classify into one or more distinct illnesses. Moreover, several different diagnoses might provide plausible explanations for some of the specific health complaints. It has thus been difficult to develop a case definition (that is, a reliable way to identify individuals with a specific disease), which is a criterion for doing effective epidemiological research.

In summary, the ongoing epidemiological research will not be able to provide precise, accurate, and conclusive answers regarding the causes of veterans' illnesses because of these formidable methodological problems.

Support for Key Government Conclusions Is Weak or Subject to Alternative Interpretations

Six years after the war, little is conclusively known about the causes of Gulf War veterans' illnesses. In the absence of official conclusions from DOD and VA, we examined conclusions drawn in December 1996 by the Presidential Advisory Committee on Gulf War Veterans' Illnesses. This Committee was established by the President to review the administration's activities regarding Gulf War veterans' illnesses. In January 1997, DOD endorsed the Committee's conclusions about the likelihood that exposure to 10 commonly cited agents contributed to the explained and unexplained illnesses of these veterans. We found that the evidence to support three of these conclusions is either weak or subject to alternative interpretations.

First, the Committee concluded that “stress is likely to be an important contributing factor to the broad range of illnesses currently being reported by Gulf War veterans.” While stress can induce physical illness, the link between stress and these veterans’ physical symptoms has not been firmly established. For example, a large-scale, federally funded study concluded that “for those veterans who deployed to the Gulf War and currently report physical symptoms, neither stress nor exposure to combat or its aftermath bear much relationship to their distress.”¹⁰

The Committee has stated that “epidemiological studies to assess the effects of stress invariably have found higher rates of posttraumatic stress disorder (PTSD) in Gulf War veterans than among individuals in nondeployed units or in the general U.S. population of the same age.” Our review indicated that the prevalence of PTSD among Gulf War veterans may be overestimated due to problems in the methods used to identify it. Specifically, the studies on PTSD to which the Committee refers have not excluded other conditions, such as neurological disorders that produce symptoms similar to PTSD and can also elevate scores on key measures of PTSD. Also, the use of broad and heterogeneous groups of diagnoses (e.g., “psychological conditions”—ranging from tension headache to major depression) in data from DOD’s clinical program may contribute to overestimation of the extent of serious psychological illnesses among Gulf War veterans.

Second, the Committee concluded that “it is unlikely that infectious diseases endemic to the Gulf region are responsible for long term health effects in Gulf War veterans, except in a small known number of individuals.” Similarly, PGVCB concluded that because of the small number of reported cases “the likelihood of leishmania tropica as an important risk factor for widely reported illness has diminished.” While this is the case for observed symptomatic infection with the parasite, the prevalence of asymptomatic infection is unknown, and such infection may reemerge in cases in which the patient’s immune system becomes deficient. As the Committee noted, the infection may remain dormant up to 20 years. Because of this long latency, the infected population is hidden, and because even classic forms of leishmaniasis are difficult to recognize, we believe that leishmania should be retained as a potential risk factor for individuals who suffer from immune deficiency.

¹⁰R. H. Stretch et al., “Physical Health Symptomatology of Gulf War-era Service Personnel From the States of Pennsylvania and Hawaii, *Military Medicine*, vol. 160 (1995), pp. 131-136.

Third, the Committee also concluded that it is unlikely that the health effects reported by many Gulf War veterans were the result of (1) biological or chemical warfare agents, (2) depleted uranium, (3) oil-well fire smoke, (4) pesticides, (5) petroleum products, and (6) pyridostigmine bromide or vaccines. However, our review of the Committee's conclusions indicated the following:

- While the government found no evidence that biological weapons were deployed during the Gulf War, the United States lacked the capability to promptly detect biological agents, and the effects of one agent, aflatoxin, would not be observed for many years.
- Evidence from various sources indicates that chemical agents were present at Khamisiyah, Iraq, and elsewhere on the battlefield. The magnitude of the exposure to chemical agents has not been fully resolved. As we recently reported, 16 of 21 sites categorized by Gulf War planners as nuclear, biological, and chemical (NBC) facilities were destroyed. However, the United Nations Special Commission found after the war that not all the possible NBC targets had been identified by U.S. planners. The Commission has investigated a large number of the facilities suspected by the U.S. authorities as being NBC related. Regarding those the Commission has not yet inspected, we determined that each was attacked by coalition aircraft during the Gulf War. One of these sites is located within the Kuwait theater of operations in close proximity to the border, where coalition ground forces were located.¹¹
- Exposure to certain pesticides can induce a delayed neurological condition without causing immediate symptoms.
- Available research indicates that exposure to agents like pyridostigmine bromide can alter the metabolism of organophosphates (the chemical family of some pesticides that were used in the Gulf War, as well as certain chemical warfare agents) in ways that enhance chronic effects on the brain.

Recommendations to the Secretaries of Defense and Veterans Affairs

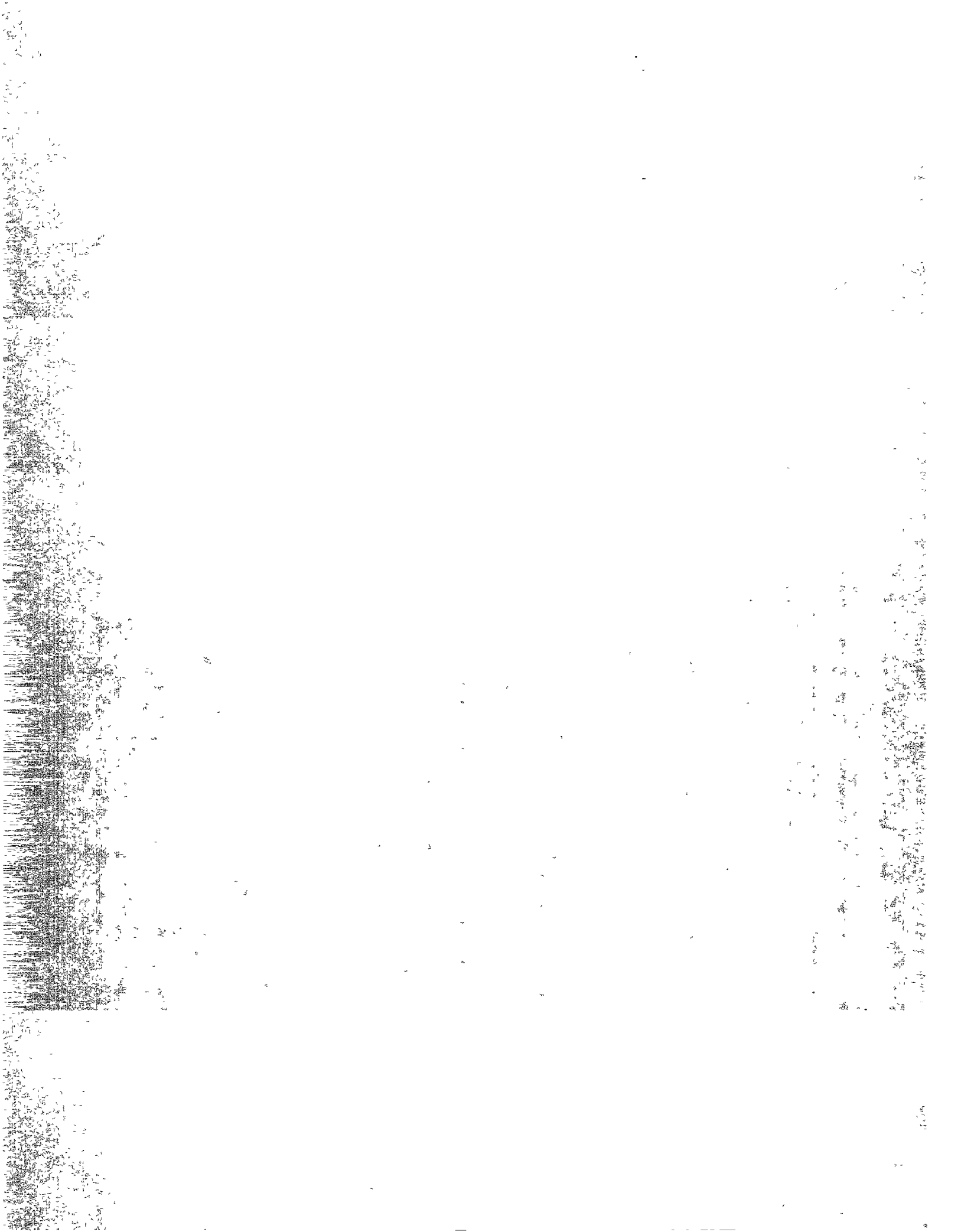
Because of the numbers of Gulf War veterans who continue to experience illnesses that may be related to their service during the Gulf War, we recommended in our report that the Secretary of Defense, with the Secretary of Veterans Affairs, (1) set up a plan for monitoring the clinical progress of Gulf War veterans to help promote effective treatment and better direct the research agenda and (2) give greater priority to research on effective treatment for ill veterans and on low-level exposures to

¹¹Operation Desert Storm: Evaluation of the Air Campaign (GAO/NSIAD-97-134, June 12, 1997), p. 2.

chemicals and their interactive effects and less priority to further epidemiological studies.

We also recommended that the Secretaries of Defense and Veterans Affairs refine the current approaches of the clinical and research programs for diagnosing posttraumatic stress disorder consistent with suggestions recently made by the Institute of Medicine. The Institute noted the need for improved documentation of screening procedures and patient histories (including occupational and environmental exposures) and the importance of ruling out alternative causes of impairment.

Mr. Chairman, that concludes our prepared statement. We will be happy to answer any questions you or members of the Subcommittee may have.



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